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Plaque Distribution Patterns in Distal Left Main Coronary Artery to Predict Outcomes After Stent Implantation

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Objectives The aim of this study was to investigate the association between plaque distribution at left main (LM) bifurcation and target lesion revascularization (TLR) after stenting.

Background Despite favorable reported mid- and long-term results, stent implantation on LM bifurcation remains challenging. The role of atherosclerotic plaque distribution in affecting LM bifurcation stenting outcomes has not been explored.

Methods A total of 329 patients undergoing LM bifurcation stenting in 2 centers were included. A method based on different plaque locations within the bifurcation area was applied. The overall population was divided in 2 groups according to the presence of a specific pattern characterized by plaque occupying (n = 145) or not occupying (n = 184) the whole bifurcation (WB) area.

Results Baseline clinical, angiographic, and procedural characteristics were well-balanced between the 2 groups. The WB group showed a significantly higher risk of 3-year TLR compared with the non-WB group (24.9% vs. 8.3%; unadjusted hazard ratio: 3.12; 95% confidence interval: 1.59 to 6.11; p = 0.001; adjusted hazard ratio: 2.84; 95% confidence interval: 1.43 to 5.64; p = 0.003). The 3-year TLR rate was not significantly different between patients treated with 1-or 2-stent techniques either in the WB or non-WB groups. In the WB group, TLR was similar between patients with lesions classified as 1,1,1 and non–1,1,1 by the Medina classification (20.7% vs. 26.8%, p = 0.57, respectively).

Conclusions The WB pattern is associated with enhanced TLR risk, regardless of stent technique and plaque severity. This could impact the treatment strategy of high-risk lesions involving the whole bifurcation area. (J Am Coll Cardiol Intv 2010;3:624–31) © 2010 by the American College of Cardiology Foundation

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Current guidelines consider surgery as the "gold standard" for unprotected left main (LM) coronary artery disease (1,2). However, percutaneous treatment of LM disease has increased over the last few years (3). Several studies have shown that stenting in LM, especially by using drug-eluting stents (DES), is a safe and effective treatment strategy, both at mid- and long-term follow-up (4–7). Moreover, several observational registries, a small randomized study, and a

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subgroup analysis from a recent randomized study of DES versus coronary artery bypass grafting (CABG) in LM and/or 3-vessel disease, have shown DES to provide results comparable to CABG (8–12). Despite these promising mid- and long-term results and the availability of DES, which several studies have shown to markedly improve LM stenting outcomes compared with bare-metal stents (BMS) (13–15), stenting on LM bifurcation remains challenging and provides less optimal outcomes than those achieved after non-distal LM stenting (16–18). Possible contributing factors to this shortcoming of LM bifurcation stenting might include intrinsic anatomical and hemodynamic characteristics along with technique-related issues. The specific distribution pattern of the atherosclerotic plaque, which embraces a broad spectrum of localizations in the different segments composing the bifurcation, might be another important factor. However, the impact of plaque distribution at LM bifurcation on outcomes after stenting is unknown. The purpose of this study was to investigate on a possible independent association between a specific plaque distribution within the LM bifurcation area and long-term outcomes after percutaneous coronary intervention (PCI) with stenting.

Methods

Patient population. Demographic and procedural data regarding all patients undergoing stent implantation for unprotected LM coronary artery disease in 2 Italian centers have been prospectively entered into a dedicated ongoing database. Patients who underwent stent implantation for de novo significant (≥50%) lesions located at LM bifurcation between June 2002 and December 2008 were included in this study. Conversely, patients treated after December 2008 were excluded, because only patients with a minimum follow-up of 6 months were considered for the purposes of the present analysis. Patients undergoing DES or BMS implantation were included. Patients were treated with 1- or 2-stent techniques at operator's discretion. All patients were fully informed about the possible procedure-related risks and the alternative treatment options, and written informed consent was obtained in all cases.

Definition of LM bifurcation and characterization of plaque distribution patterns. Two transversal planes, the first crossing the take-off of the left circumflex (LCX) and the second crossing the point of bifurcation, were considered to define the bifurcation as the area included between 2 mm above and below the first and the second plane, respectively (Fig. 1). Following this approach, in the bifurcation area 3 "regions" were identified: 1 above the first plane; 1 included between the first and second planes; and the other 1 below the second plane.

Within these 3 "regions," we identified the possible different plaque locations at the 3 "sides" of the bifurcation: through LM–left anterior descending (LAD); through LM-LCX, and at the point of bifurcation. Combining these possible plaque locations at each of the 3 "sides," several different plaque distribution patterns could be identified (Fig. 1). Among them, the pattern in which the plaque is located at all 3 bifurcation "regions" and at each of the 3 considered "sides," defined as "whole bifurcation involvement" (WB), accounted for almost one-half of the population by itself. Due to the low relative number of cases within each of the several remaining patterns that would be derived by combining the possible plaque locations at each of the 3 "sides" and to allow for a simplified binary approach, 1 single group for comparison with the WB pattern was considered and referred as "partial bifurcation involvement" (non-WB) group. Case examples of WB and non-WB plaque distribution patterns as assessed by angiography are shown in Figure 2.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CABG = coronary artery bypass grafting
DES = drug-eluting stent(s)
LAD = left anterior descending
LCX = left circumflex
LM = left main
PCI = percutaneous coronary intervention
TLR = target lesion revascularization
WB = whole bifurcation

The presence of the plaque at each side was attributed regardless of the stenosis degree. However, the overall narrowing was ≥50% in at least 1 point of the specified bifurcation area, considering the entire bifurcation. The plaque distribution pattern was evaluated for each bifurcation by angiographic analysis. Intravascular ultrasound plaque distribution evaluation was not performed for the purposes of this exploratory analysis. Plaque distribution pattern in each bifurcation was evaluated in 2 orthogonal angiographic views and characterized as described in the preceding text. The angiographic analysis was performed offline by 2 experienced observers blinded to study outcomes. In case of disagreement, the opinion of a third observer was obtained, and the final decision was made by consensus. Interobserver and intraobserver variability of the binary plaque assessment (WB or non-WB plaque involvement) were 12% and 7%, respectively. Coronary angiograms

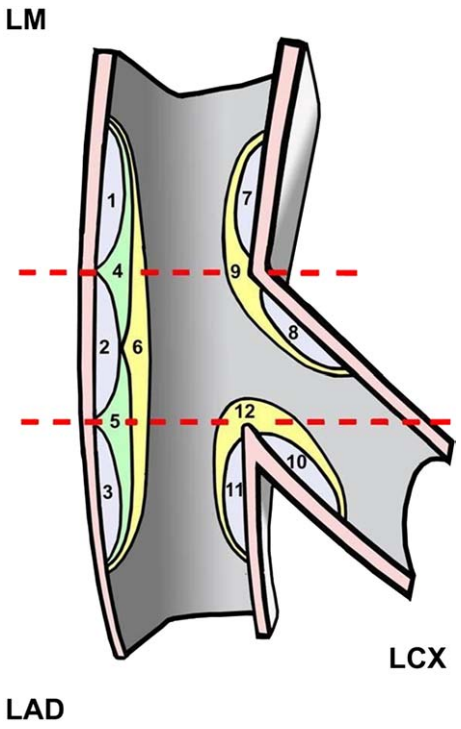

Figure 1. Description of All Possible Plaque Locations at the LM Bifurcation Area

All potential locations, which were evaluated in the angiogram, are sequentially numbered. The presence of plaque was evaluated in 3 "regions," at 3 "sides." The "regions" were: within 2 mm above the first plane; within 2 mm below the second; and between the 2 pre-defined planes. The "sides" were: through left main (LM)–left anterior descending (LAD); through LM-left circumflex (LCX); and the point of bifurcation. The whole bifurcation pattern comprises the locations indicated at 6, 9, and 12. The location 12 does not indicate the carinal plaque involvement, but schematically indicates the plaque involvement of both left main branches below the plane crossing the point of bifurcation, as evaluated by angiography. All the remaining plaque location combinations account for the non–whole bifurcation pattern.

obtained at baseline and after the stenting procedure were analyzed with a validated program (QCA-CMS version 6.0, Medis Medical Imaging Systems, Leiden, the Netherlands).

End point definition. Clinical follow-up for all patients was scheduled at 1, 6, and 12 months and every 6 months after the first year and performed by outpatient visits or telephone interviews. Information about clinical status, change in medical management, and occurrence of any adverse event were recorded. Medical records of patients hospitalized during the follow-up period were obtained to adjudicate adverse events. Adjudication of adverse outcomes was performed by physicians not involved with the interventional procedures. Angiographic follow-up was recommended between 6 and 12 months or earlier if clinically indicated by symptoms or documented myocardial ischemia. The primary outcome measure of this analysis was target lesion revascularization (TLR) defined as any repeat intervention (by CABG or PCI) performed to treat a stenosis inside the implanted stent or within the 5-mm segments adjacent to the stent or involving the ostium of LAD and/or LCX coronary arteries. In addition, to account for the chance of biases introduced by disproportionate competing end points, such as mortality, a composite end point of all-cause death and TLR was considered.

Statistical analysis. Continuous variables were analyzed for a normal distribution with the Kolmogorov-Smirnov test and presented as mean ± SD or median and interquartile range, as appropriate. *t* tests were used for comparison of normally distributed continuous variables. Mann-Whitney rank sum tests were used for comparisons of continuous variables not following a normal distribution. Categorical variables were expressed as frequencies and percentages. Chi-square or Fisher exact tests were used for comparisons of categorical variables. Rates of TLR were expressed as Kaplan-Meier estimates at 36 months and compared with log-rank testing. Cox proportional hazards regression model was used to assess the risk of TLR associated with the WB distribution pattern.

Multivariable analysis was used to account for potential confounders. Covariates with a plausible association with TLR (diabetes, stent technique, use of DES, reference vessel diameter, lesion length, and post-procedure minimal lumen diameter according to main and side branches) were entered in the multivariable Cox model and those that were not significant at $p < 0.10$ were removed by a backward stepwise elimination. In the final model of significant covariates, including the side branch reference vessel diameter and the post-procedure main and side branches minimal lumen diameter, plaque distribution was added as independent binary variable (WB or non-WB). The assumption of proportional hazard was checked with time-dependent covariates and found to be reasonable. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A p value <0.05 was considered statistically significant. Bonferroni correction was applied for comparisons between plaque distribution patterns performed after stratification by bifurcation stenting technique (1-stent or 2-stent). Statistical analysis was performed with the SPSS version 15.0 software (SPSS, Inc., Chicago, Illinois).

Results

Plaque distribution and patient characteristics. A total of 329 patients undergoing stent implantation in LM bifurcation lesions were evaluated. The WB pattern was found in 145 (44.1%) lesions. The WB and non-WB groups were well-balanced with respect to the baseline clinical (Table 1) and procedural (Table 2) characteristics, with the only significant difference being in the stent techniques performed.

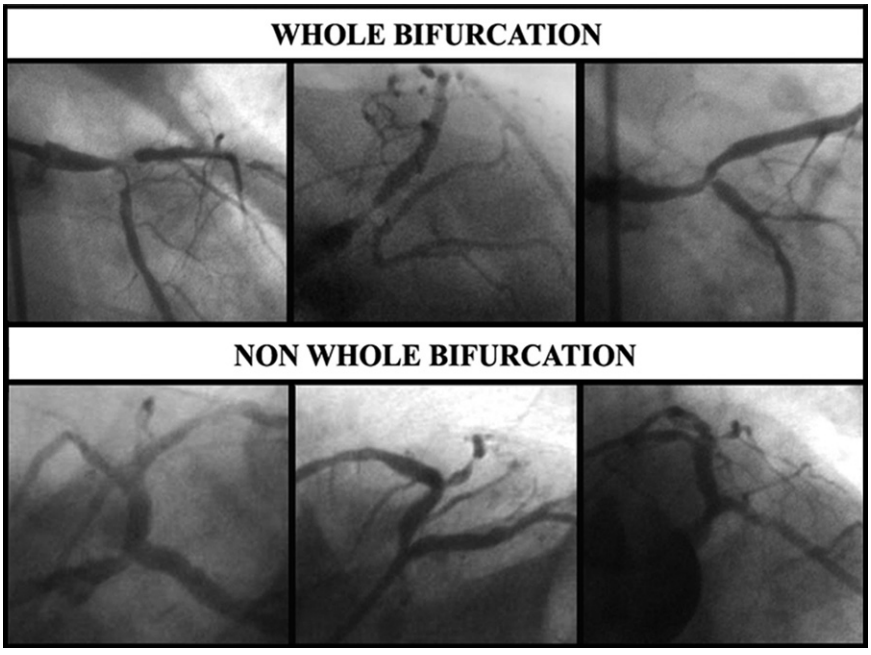

Figure 2. Angiograms With the 2 Assessed Plaque Distribution Patterns

At the **top** the 3 angiograms were characterized as whole bifurcation plaque pattern, and those 3 at the **bottom** were characterized as non–whole bifurcation plaque pattern.

Quantitative coronary angiographic analysis results for both the main (LM-LAD) and the side branch (LCX) at baseline and after the procedure are summarized in Table 3, according to the plaque distribution patterns. Quantitative data were similar between the 2 evaluated groups, except for a trend toward smaller baseline minimal lumen diameter and lower stenosis degree of the side branch in the non-WB group.

Plaque distribution and outcomes. Clinical follow-up of at least 6 months was available in 100% of all surviving patients. Angiographic follow-up was performed in 72.2% and 70.6% of patients in the WB and non-WB groups, respectively. At 3-year follow-up, 41 (12.5%) patients required a TLR. Of them, 29 (70.7%) were performed in bifurcation lesions with a WB distribution. The WB group was at significantly higher risk of 3-year TLR compared with the non-WB group (24.9% vs. 8.3%; HR: 3.12; 95% CI: 1.59 to 6.11; p = 0.001) (Fig. 3). The incidence of the

Table 1. Baseline Clinical Characteristics

Variables	WB Group (n = 145)	Non-WB Group (n = 184)	p Value
Age (yrs)	68.5 ± 10.2	66.3 ± 10.3	0.07
Male	119 (82)	142 (77)	0.34
Risk factors			
Hypertension	106 (73)	144 (78)	0.34
Hyperlipidemia	108 (74)	120 (65)	0.09
Diabetes	48 (33)	59 (32)	0.94
Current smokers	39 (27)	41 (22)	0.40
Clinical presentation			
Stable angina	52 (36)	63 (34)	0.85
Unstable angina/NSTEMI	90 (62)	112 (61)	0.91
STEMI	3 (2)	9 (5)	0.29

Values shown as mean ± SD or n (%).
NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; WB = whole bifurcation.

Table 2. Baseline Procedural Characteristics

Variables	WB Group (n = 145)	Non-WB Group (n = 184)	p Value
Bare-metal stents	9 (6)	7 (4)	0.46
Drug-eluting stents	136 (94)	177 (96)	0.46
Maximal inflation pressure (atm)	19.3 ± 2.9	18.9 ± 3.1	0.23
Glycoprotein IIb/IIIa inhibitor use	30 (21)	35 (19)	0.66
Intra-aortic balloon pump	6 (4)	3 (2)	0.30
Rotablator	5 (3)	3 (2)	0.48
Intravascular ultrasound	16 (11)	15 (8)	0.48
Technique			0.001
Provisional T-stenting	70 (48)	123 (67)	
T-stenting	38 (26)	37 (20)	
V-stenting	3 (2)	7 (4)	
Mini crush stenting	34 (23)	17 (9)	
Final kissing balloon	140 (97)	170 (92)	0.17

Values shown as mean ± SD or n (%).
Abbreviation as in Table 1.

Table 3. Quantitative Coronary Angiography

	Main Branch (LM-LAD)			Side Branch (LCX)		
	WB	Non-WB	p Value	WB	Non-WB	p Value
Baseline angiography, n	145	184		145	184	
Reference vessel diameter (mm)	3.51 (3.15–3.62)	3.52 (3.08–3.56)	0.30	3.11 (2.75–3.25)	3.10 (2.75–3.50)	0.48
Minimum lumen diameter (mm)	1.08 (0.81–1.40)	1.06 (0.86–1.39)	0.92	1.40 (1.08–1.77)	1.58 (1.05–2.00)	0.05
Diameter stenosis (%)	69.3 (60.0–75.4)	69.4 (60.2–74.5)	0.98	55.0 (43.4–60.3)	51.8 (34.6–63.8)	0.07
Lesion length (mm)	16.0 (10.2–21.3)	16.2 (10.5–22.1)	0.87	9.2 (6.1–11.6)	9.6 (6.0–13.2)	0.83
Post-procedural angiography, n	145	184		145	184	
Reference vessel diameter (mm)	3.54 (3.20–3.64)	3.54 (3.15–3.70)	0.81	3.15 (2.80–3.45)	3.13 (2.89–3.53)	0.44
Minimum lumen diameter (mm)	3.16 (2.85–3.33)	3.19 (2.84–3.41)	0.53	2.85 (2.50–3.07)	2.85 (2.58–3.23)	0.55
Diameter stenosis (%)	10.4 (8.0–11.8)	9.1 (6.9–11.9)	0.10	6.7 (5.3–12.6)	8.8 (5.8–11.4)	0.40

Values are presented as median (interquartile range).
LCX = left circumflex; LM-LAD = left main–left anterior descending; other abbreviation as in Table 1.

composite end point of all-cause death and TLR was significantly higher in the WB group (32.2% vs. 20.2%; HR: 1.76; 95% CI: 1.10 to 2.83; p = 0.02). After adjustment, the WB distribution pattern remained significantly associated with TLR (adjusted HR: 2.84; 95% CI: 1.43 to 5.64; p = 0.003) and the composite end point of all-cause death and TLR (adjusted HR: 1.79; 95% CI: 1.11 to 2.91; p = 0.018). There was no independent association between stent technique and TLR (adjusted HR: 1.48; 95% CI: 0.79 to 2.79; p = 0.22).

In the WB group, there were no significant differences in the 3-year TLR rates between patients treated with 1-stent (n = 69; 47.6%) and 2-stent (n = 76; 52.4%) techniques (22.3% vs. 26.9%, p = 0.29, respectively) (Fig. 4). Similarly, no significant difference in the 3-year TLR rates were observed between patients treated with 1-stent (n = 123; 66.8%) and 2-stent (n = 61; 33.2%) techniques in the non-WB group (7.5% vs. 10.1%, p = 0.55, respectively) (Fig. 4). The TLR rates were significantly different between WB and non-WB patterns both in the 1-stent (p = 0.028) and 2-stent (p = 0.023) technique subgroups (Fig. 4). When applying the Bonferroni correction, the difference in the TLR rates between WB and non-WB patterns reached the limits of statistical significance both within the 1-stent (p = 0.056) and the 2-stent (p = 0.046) technique subgroups. A significant independent association between WB distribution and TLR was consistently observed either in 1-stent (adjusted HR: 2.68; 95% CI: 1.04 to 6.93;

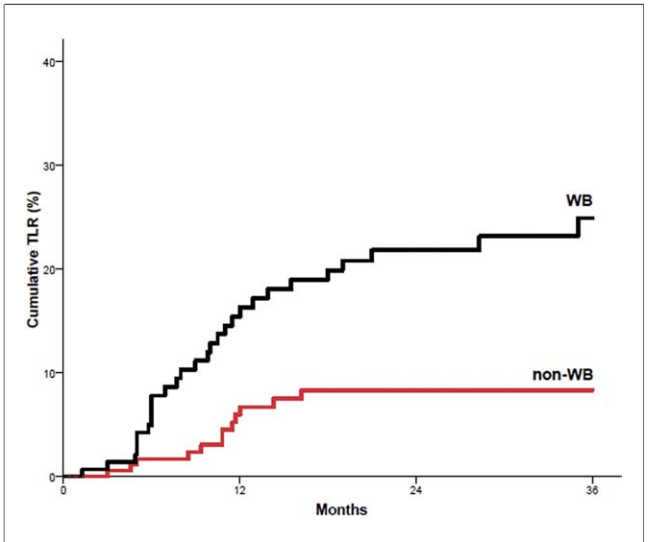

Figure 3. Kaplan-Meier Curves for WB and Non-WB Groups

Cumulative 3-year rates of target lesion revascularization (TLR) in the whole bifurcation (WB) and non-WB groups. **Black line** = WB. **Red line** = non-WB.

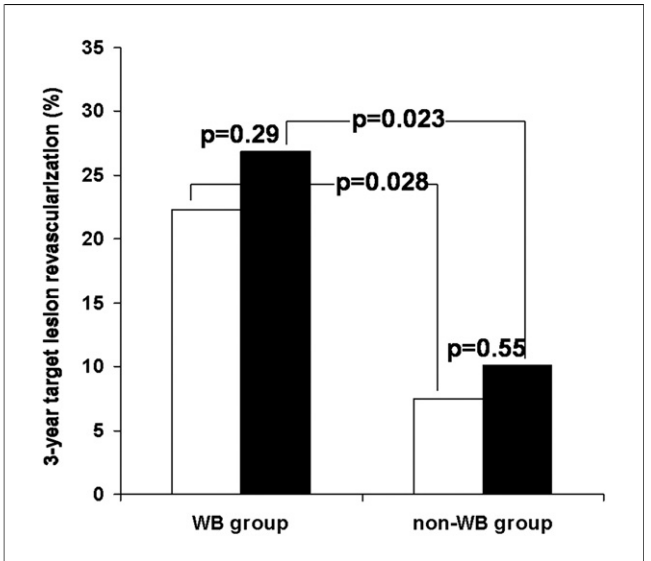

Figure 4. Rates of 3-Year TLR Within the WB and Non-WB Groups According to the Stent Technique

Three-year TLR in groups treated with 1-stent or 2-stent techniques within the WB and non-WB groups. **Open bars** = 1-stent technique. **Solid bars** = 2-stent technique. Abbreviations as in Figure 3.

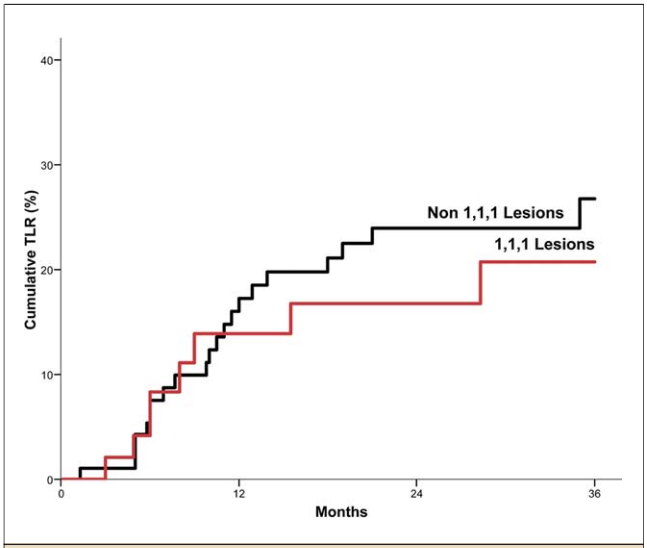

Figure 5. Kaplan-Meier Curves for Subgroups With Lesions Classified as 1,1,1 and Non–1,1,1, According to Medina Classification, Within the WB Group

Cumulative 3-year rates of TLR in subgroups with 1,1,1 and non–1,1,1 lesions, classified according Medina classification. **Black line** = non–1,1,1 lesions. **Red line** = 1,1,1 lesions. Abbreviations as in Figure 3.

p = 0.04) or 2-stent (adjusted HR: 3.04; 95% CI: 1.28 to 8.18; p = 0.028) treated patients.

Among WB lesions, 33.8% and 66.2% were classified as 1,1,1 and non–1,1,1 according to the Medina classification, respectively. Up to 3 years, the incidence of TLR was similar between these groups (20.7% in 1,1,1 vs. 26.8% in non–1,1,1; p = 0.57) (Fig. 5). Among lesions classified as non–1,1,1 by the Medina classification, the cumulative 3-year TLR rate was still significantly higher in the WB compared with the non-WB group (26.8% vs. 7.8%, p = 0.0003) (Fig. 6).

Discussion

Despite across-the-board promising outcomes after stenting for LM disease, the LM bifurcation lesions remain challenging, and their restenosis rate is still high, even with DES. This could be attributed to several factors, including anatomical, hemodynamic, and technical issues. This is the first study evaluating the impact on long-term TLR of atherosclerotic plaque distribution within the LM bifurcation area.

Applying a novel approach for studying LM bifurcation lesions, we observed that the location of the plaque within the bifurcation area is fairly heterogeneous, with a single specific plaque setting—namely WB—accounting for approximately 50% of the overall lesion patterns. Importantly, this frequent plaque distribution pattern was associated with higher risk of TLR throughout 3 years of follow-up, independently of the angiographic characteristics, including stenosis degree, vessels and lesions treated, and stent technique performed. Therefore, within the overall LM bifurcation lesions subset, a specific "high-risk bifurcation type" was identified, on the basis of its particular "high-risk plaque distribution." This finding suggests that not all of the LM bifurcation lesions are the same, but there is "the good bifurcation and the bad bifurcation." The reason why a WB compared with a non-WB bifurcation is associated with enhanced need of reintervention, regardless of stent strategy and disease severity, is not so obvious. We can hypothesize that, in the WB distribution, a greater burden of plaque occupying extensively all the segments of the main components of the bifurcation might cause hemodynamic alterations of flow patterns favoring the intimal hyperplasia after stent implantation. Interestingly, the specific plaque location of WB pattern might represent a particular anatomic condition upsetting the stent deployment and thus potentially favoring disease progression in a type of plaque that also might have an enhanced inherent propensity to progress.

Many classifications systems for bifurcation lesions have been proposed (19,20), but the Medina classification is the most-adopted, due to its simplicity (19). However, in the setting of LM, the prognostic implications of this classification and its applicability have yet to be established. We defined a different LM bifurcation description that seems to have a pivotal prognostic value, while remaining quite simple and easy to be memorized. Within the WB group, the absence of difference in the TLR rates between lesions classified as 1,1,1 and non–1,1,1 by the Medina classifica-

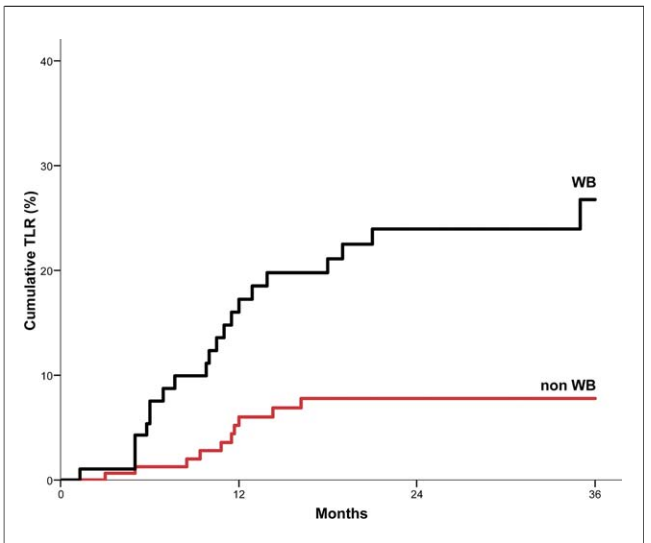

Figure 6. Kaplan-Meier Curves for WB and Non-WB Groups Within the Subgroup With Lesions Classified as Non–1,1,1, According to Medina Classification

Cumulative 3-year rates of TLR in the WB and non-WB groups, within the subgroup with lesions classified as non–1,1,1, according to Medina classification. **Black line** = WB. **Red line** = non-WB. Abbreviations as in Figure 3.

tion, emphasizes that the overall plaque distribution pattern is a negatively impacting factor, regardless of the degree of stenosis in each single segment of the bifurcation. Summarizing, on the basis of our findings, it might be stated that bifurcation lesions with the same distribution pattern have similar prognosis after stent implantation, although they could differ in terms of critical narrowing location.

Therefore, focusing on the plaque distribution, which discriminated patient at high risk of TLR, could be a useful aid for risk stratification of LM bifurcation (WB types high risk, non-WB low risk) providing important insights on "lesion selection," which is critical in the LM setting, to improve outcomes of LM percutaneous revascularization. This might be critical in selecting the treatment strategy of LM bifurcation. The significantly higher TLR rate observed in the WB group suggests that this specific type of bifurcation could benefit from a more optimal percutaneous strategy or a surgical rather than percutaneous revascularization treatment.

Study limitations. This was an observational study and therefore suffers from limitations inherent in its retrospective design. Intravascular ultrasound, which could overcome the well-known limitations of angiography in precisely assessing plaque distribution, was not routinely performed. However, angiography is still the most practical and broadly accepted method to characterize coronary lesions.

Another caveat is that, although this study showed that plaque distribution pattern predicted outcome regardless of the stent technique performed, the impact of this latter factor should be better evaluated in a larger population with more clinical events and a pre-specified design.

Finally, the WB and non-WB distribution classification system was derived by collapsing all the potential plaque distribution pattern frequencies in a binary, simplified, and practical fashion. This binary approach has been developed "ad hoc," secondary to findings observed in a single contemporary group of patients, without pre-specifying the binary division itself. Consequently, the prognostic value of this proposed binary plaque distribution system cannot be considered fully validated until the present results are reproduced in a different array of patients (21).

Conclusions

We identified, with a simple binary method based on the plaque distribution within the bifurcation area, a particular distribution pattern associated with enhanced long-term TLR risk compared with all the other patterns, regardless of stent technique and plaque severity. These findings could have an impact on the treatment strategy of this high-risk lesions subset. This approach, which was found to be associated with outcomes after LM stenting, could turn out useful in interventional practice when dealing with challenging lesions, such as LM bifurcations. However, the findings of the present exploratory analysis would need to be replicated before being considered definitive (19).

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